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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/284,787	08/16/1999	THOMAS EMRICH	BMID9913US	2784

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EXAMINER	
ZEMAN, ROBERT A	
ART UNIT	PAPER NUMBER
1645	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/03/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/284,787	EMRICH ET AL.	
	Examiner	Art Unit	
	Robert A. Zeman	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 June 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *22-27* is/are allowed.

6)☒ Claim(s) *18-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment and response filed on 6-2-2006 are acknowledged. Claims 18-19 and 22-23 have been amended. Claims 26-27 have been added. Claims 18-27 are pending and currently under examination.

Claim Rejections Withdrawn

The rejection of claim 22 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the phrase "**A** monoclonal antibody produced by hybridoma..." is withdrawn in light of the amendment thereto.

The rejection of claims 18 and 19 rendered vague and indefinite by the recitation of the tradename BIOCORE® is withdrawn in light of the amendment thereto.

Claim Rejections Maintained

35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless —
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of claims 18-21 under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Hinds et al. (Journal of Medicinal Chemistry, 1991 Vol. 34, No. 6, pages 1777-1789 - IDS-6) for reasons set forth in the previous Office action.

Applicant argues:

1. The two monoclonal antibodies (DB19/1 and DB19/25) isolated by Hinds et al. have dissociation constants of 1.8×10^{-7} and 1.8×10^{-8}. Hence, Hinds et al. fails to teach an isolated antibody with the required binding affinity.

2. The instant claims have been amended to state that the claimed antibody binds with an affinity greater than $3 \times 10^{8} M^{-1}$ to a 13 or 14 amino acid sequence that includes a nine amino acid sequence consisting of YPYDVPDYA.

3. The possibility that the methods disclosed by Hinds could generate antibodies having the high affinities of applicant's claimed antibodies is mere speculation.

4. Contrary to the Examiner's assertion, one of ordinary skill in the art would not anticipate antibodies with the claimed affinity would be generated for each antigen subjected to standard antibody production procedures.

5. The ability of producing the high affinity antibodies of the present invention could not have been expected and therefore cannot be obvious, absent specific evidence showing they can be produced. However, the techniques for producing antibodies are sufficiently well characterized that the results are **reproducible once an antigen has been characterized.**

6. "Obvious to try" is not the standard under 35 U.S.C. 103(a).

Applicant's arguments have been fully considered and deemed non-persuasive.

With regard to Points 1 and 2, Applicant's arguments have been fully considered and deemed non-persuasive. Table IV of the cited reference, monoclonal antibody DB19/1 has dissociation constants to peptides containing the sequence YPYDVPDYA ranging from 8.8 x 10^{-5} to 3.6 x10^{-9} whereas monoclonal antibody DB19/25 has dissociation constants to the same peptides ranging from 1.8 x 10^{-6} to 5.7 x10^{-9}. Consequently, said antibodies do possess the same binding affinities of the antibodies of the instant invention. Applicant's arguments regarding methylation is not persuasive as the claims only have to have an affinity for YPYDVPDYA.

With regard to Points 3-5, as Applicant has pointed out the "epitope" YPYDVPDYA is well characterized and hence standard antibody production methodologies would necessarily produce antibodies with the claimed affinities as binding affinity is predicated on the immunoepitopes to which it binds.

As outlined previously, the instant claims are drawn to monoclonal antibodies with a binding affinity greater than 3 x 10^8M^{-1} for the amino acid sequence of YPYDVPDYA. Hinds et al. disclose antibodies with a binding specificity to the sequence YPYDVPDYA (see abstract). Although Hinds et al. disclose the same product they do not disclose the claimed method of making. However, it should be noted that the instant claims constitute Product-by-Process type claims. In Product-by-Process type claims, the process of producing the product is given no patentable weight since it does not impart novelty to a product when the product is taught by the prior art. See *In re Thorpe*, 227 USPQ 964 (CAFC 1985); *In re Marosi*, 218 USPQ 289, 292-293 (CAFC 1983) and *In re Brown*, 173 USPQ 685 (CCPA 1972). Consequently, even if a particular process used to prepare a product is novel and unobvious over the prior art, the product *per se*, even when limited to the particular process, is unpatentable over the same product taught in by the prior art. See *In re King*, 107 F.2d 618, 620, 43 USPQ 400, 402 (CCPA 1939); *In re Merz*, 97 F.2d 599, 601, 38 USPQ 143-145 (CCPA 1938); *In re Bergy*, 563 F.2d 1031, 1035, 195 USPQ 344, 348 (CCPA 1977) *vacated* 438 US 902 (1978); and *United States v. Ciba-Geigy Corp.*, 508 F. Supp. 1157, 1171, 211 USPQ 529, 543 (DNJ 1979). Finally, since the Patent Office does not have the facilities for examining and comparing Applicant's composition with the compositions of the prior art reference, the burden is upon Applicant to show a distinction between the material, structural and functional char acteristics of the claimed composition and the composition of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

With regard to Applicant's assertion that Hinds et al does not render instant invention obvious, said methods are standard practice in the art. Moreover, for antibodies specific for a given antigen, the K_d usually varies from about 10^{-7} M to 10^{-11}M (see Cellular and Molecular Immunology,

page 54). Therefore since Hinds et al. disclose antibodies with a binding specificity to the sequence YPYDVPDYA (see abstract), some of said antibodies would have the requisite affinities. Additionally, it would be obvious to one of skill in the art to select those antibodies with the highest affinities.

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 18-21 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained for reasons of record. The rejection of claims 23 and 25 is withdrawn in light of the amendment to claim 23. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejected claims are drawn to monoclonal antibodies with a binding affinity of greater than 3 x $10^{8}M^{-1}$ to $10^{10}M^{-1}$ for the amino acid sequence of YPYDVPDYA wherein the antigen utilized to produce said monoclonal antibodies is haemagglutinin peptide consisting of 13 or 14 amino acids wherein a nine amino acid sequence of said epitope consists of the sequence YPYDVPDYA.

Applicant argues that they have "fully characterized" the antigen to which the claimed

antibodies are raised (i.e. a keyhole limpet hemocyanin (KHL)-coupled haemagglutinin protein (comprising either SEQ ID NO:2 or SEQ ID NO:3 as the HA protein). Applicant further argues that they have reduced to practice 3 specific clones.

Applicant's arguments have been fully considered and deemed non-persuasive. Contrary to Applicant's assertion, they have not fully characterized the antigen against which the claimed antibodies were raised. The claimed "antigen" encompasses **any** 13mer or 14mer that contains the sequence YPYDVPDYA. Since the tertiary and quantinary structure of said antibody can be radically affected by the nature of the amino acids flanking the sequence, Applicant has not provide any correlation between structure (i.e. sequence) and function (i.e. binding to peptides comprising the sequence YPYDVPDYA with the recited affinities). Moreover, the rejected claims do not describe the "antigen" in terms of SEQ ID NO:2 or SEQ ID NO:3.

As outlined previously, to fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the specification must describe at least a substantial number of the members of the claimed genus, or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and distinguish its members from others, so as to reasonably convey to the skilled artisan that Applicant has possession the claimed invention. To adequately describe the genus of antibodies with a binding affinity greater than $3 \times 10^{8}M^{-1}$ to $10^{10}M^{-1}$ for the amino acid sequence of YPYDVPDYA, one must describe the antigenic determinants (immunoepitopes) of the antigen (haemagglutinin peptide) that induces antibodies with the claimed binding affinity.

Aside from SEQ ID NO:2 and 3, the specification does not describe with any degree of

specificity members of the genus of haemagglutinin 13mer or 14mer peptides to which the members of the claimed genus of antibodies must bind, wherein said antibodies a binding affinity of 10^8M^{-1} to $10^{10}M^{-1}$ for the amino acid sequence of YPYDVPDYA such that the specification might reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Moreover, the specification does not disclose distinguishing and identifying features of a representative number of members of the genus of antibodies to which the claims are drawn, such as a correlation between the structure of the immunoepitope its recited function (a binding affinity of 10^8M^{-1} to $10^{10}M^{-1}$ for the amino acid sequence of YPYDVPDYA), so that the skilled artisan could immediately envision, or recognize at least a substantial number of members of the claimed genus of antibodies. Additionally, the specification fails to disclose which amino acid residues are essential to the function of the immunoepitope or which amino acids might be replaced so that the resultant immunoepitope retains the activity of its parent, or by which other amino acids the essential amino acids might be replaced so that the resultant immunoepitope retains the activity of its parent. Therefore, since the specification fails to adequately describe at least a substantial number of members of the genus of immunoepitopes on which the claims are based; the specification fails to adequately describe at least a substantial number of members of the claimed genus of antibodies with a binding affinity of 10^8M^{-1} to $10^{10}M^{-1}$ for the amino acid sequence of YPYDVPDYA.

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description'' Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing

identifying characteristics sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed.

The *Guidelines* further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. As evidenced by Greenspan et al. (*Nature Biotechnology* **7**: 936-937, 1999), defining epitopes is not as easy as it seems. Greenspan et al. recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan et al., an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Accordingly, it follows that the immunoepitopes that bind antibodies that can prevent biofilm formation can only be identified empirically. Therefore, absent a detailed and particular description of a representative number, or at least a substantial number of the members of the genus of immunoepitopes, the skilled artisan could not immediately recognize or distinguish members of the claimed genus antibodies with a binding affinity of 10^8M^{-1} to $10^{10}M^{-1}$ for the amino acid sequence of YPYDVPDYA. Therefore, because the art is unpredictable, in accordance with the *Guidelines*, the description of immunoepitopes (antigenic determinants) is not deemed representative of the genus of antibodies to which the claims refer.

Conclusion

Claims 18-21 are rejected.

Claims 22-27 are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (571) 272-0866. The examiner can normally be reached on Mon - Fri 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272 0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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ROBERT A. ZEMAN
PRIMARY EXAMINER
December 25, 2006